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Health and Environmental Effects Profile for 2-Ethoxyethanol Esters

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR 2-ETHOXYETHANOL ESTERS

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16. ABSTRACT

The Health and Environmental Effects Profile for 2-ethoxyethanol esters was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. 2-Ethoxyethanol esters has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for 2-ethoxyethanol esters is 21.1 mg/day for inhalation exposure. The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a relase as specified by CERCLA based on chronic toxicity. Existing data are insufficient to determine an RQ value for the class as a whole. An RQ of 1000 was determined for 2-ethoxyethanol acetate.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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LIST OF ABBREVIATIONS

ADI	Average daily intake
BCF	Bioconcentration factor
BOD	Biochemical oxygen demand
CNS	Central nervous system
CS	Composite score
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Median lethal dose
MEC	Minimum effective concentration
MED	Minimum effective dose
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
TLV	Threshold limit value
TWA	Time-weighted average
WS	Water solubility

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The Chemical Abstract Service (CAS) Registry numbers, molecular weights, empirical formulas, structures, and synonyms of the 2-ethoxyethanol esters considered for study in this profile are listed in Table 1-1.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Available physical properties of commercially significant 2-ethoxyethyl esters are listed below:

2-Ethoxyethyl Acetate

Description:	colorless liquid with a sweet musty pleasant odor	Verschueren, 1983
Melting point:	-61.7°C	Brown et al., 1980
Boiling point (1 atm):	156.3°C	Brown et al., 1980
Specific gravity:	0.97 (20/4°C)	Verschueren, 1983
Refractive index:	1.4058 (20°C)	Brown et al., 1980
Vapor pressure:		
at 20°C	1.2 mm Hg	Verschueren, 1983
at 20°C	2 mm Hg	Union Carbide, 1979
at 30°C	3.8 mm Hg	Verschueren, 1983
Water solubility:		
at 20°C	23 g/100 g	U.S. EPA, 1982a
at 20°C	22.9 wt %	Union Carbide, 1979
Nonaqueous solubility:	miscible with alcohol, ether, acetone, aromatic hydrocarbons	U.S. EPA, 1982a
Partition coefficient (oil/water):	1.19	U.S. EPA, 1982a
Log octanol/water partition coefficient:	0.710 (calculated)	Basak et al., 1984
Evaporation rate (butyl acetate = 1.0):	0.2	U.S. EPA, 1982a
Conversion factors (air):	1 mg/m³ = 0.19 ppm 1 ppm = 5.4 mg/m³	

TABLE 1-1

Structure, Molecular Weight, CAS Number and Empirical Formulas of 2-Ethoxyethanol Esters

2-Ethoxyethanol Ester Synonyms	CAS Number	Molecular Weight	Empirical Formula	Structure
2-Ethoxyethyl Acetate 2-ethoxyethanol, acetate acetic acid, 2-ethoxyethyl ester ethylene glycol monoethyl ether acetate ethyl glycol acetate Cellosolve acetate 1-acetoxy-2-ethoxyethane Ektasolve EE Acetate Solvent ethoxyacetate- oxytol acetate	111-15-9	132.16	$C_6H_{12}O_3$	$CH_3-CH_2-O-CH_2-CH_2-O-\overset{\overset{O}{\|}}{C}-CH_3$
2-Ethoxyethyl Acrylate 2-ethoxyethanol, acrylate acrylic acid, 2-ethoxyethyl ester ethylene glycol monoethyl ether acrylate 2-propenoic acid, 2-ethoxyethyl ester Cellolsolve acrylate 2-ethoxyethyl 2-propenoate	106-74-1	144.17	$C_7H_{12}O_3$	$CH_3-CH_2-O-CH_2-CH_2-O-\overset{\overset{O}{\|}}{C}-CH=CH_2$
2-Ethoxyethyl Methacrylate 2-propenoic acid, 2-methyl, 2-ethoxyethyl ester methacrylic acid, 2-ethoxyethyl ester	2370-63-0	158.20	$C_8H_{14}O_3$	$CH_3-CH_2-O-CH_2-CH_2-O-\overset{\overset{O}{\|}}{C}-\overset{CH_3}{\overset{\|}{C}}=CH_2$
2-Ethoxyethanol, phosphated polyphosphoric acids, 2-ethoxyethyl esters	68554-00-7	NA	NA	NA
2-Ethoxyethyl Dodecanoate ethylene glycol monoethyl ether laurate	106-13-8	272.43	$C_{16}H_{32}O_3$	$CH_3-CH_2-O-CH_2-CH_2-O-\overset{\overset{O}{\|}}{C}-(CH_2)_{10}-CH_3$

NA = Not applicable

2-Ethoxyethyl Acrylate

Melting point:	-47.3°C	Brown et al., 1980
Boiling point (1 atm):	174.1°C	Brown et al., 1980
Specific gravity:	0.9834 (20/20°C)	Brown et al., 1980
Refractive index:	1.4274 (20°C)	Brown et al., 1980
Vapor pressure:	not available	
Water solubility: at 20°C	5.5 wt %	Brown et al., 1980

2-Ethoxyethyl Methacrylate

Boiling point:	85°C (at 19 mm Hg)	Nemec and Kirch, 1981

2-Ethoxyethyl Dodecanoate

Description:	liquid	Hawley, 1977
Freezing point:	-7 to -11°C	Hawley, 1977
Specific gravity:	0.89 (25°C)	Hawley, 1977
Water solubility:	insoluble	Hawley, 1977

Chemically, contact of 2-ethoxyethyl acetate with nitrates, strong oxidizers, strong acids and strong alkalies may cause fires and explosions (U.S. EPA, 1982a). It is not reactive with water and exposure to air and light may form explosive peroxides.

1.3. PRODUCTION DATA

Production data for 1977 available from the public portion of the U.S. EPA TSCA Production File for the various 2-ethoxyethanol esters are given in Table 1-2. Current manufacturers of 2-ethoxyethyl acetate are (SRI, 1984):

Eastman Kodak	
Tennessee Eastman	Kingsport, TN
Texas Eastman	Longview, TX
Union Carbide	Seadrift, TX
ICI Americas	Bayport, TX

TABLE 1-2

Production Data from the U.S. EPA TSCA Production File

Producer (location)	Source	Production Range (lbs)
2-Ethoxyethyl Acetate		
CPS Chem.		
Oldbridge, NJ	manufacturer	none
Eastman Kodak		
Kingsport, TN	manufacturer	10-50 million
Longview, TX	manufacturer	10-50 million
Union Carbide		
South Charleston, WV	manufacturer	confidential
Port Lavaca, TX	manufacturer	confidential
Ugine Kuhlmann		
Paramus, NJ	importer	confidential
Filo Chem.		
New York, NY	importer	none
Thorson Chem.		
New York, NY	importer	<1000
Soltex Polymer		
Deer Park, TX	importer	<1000
Montedison USA		
New York, NY	importer	<1000
Ciba-Geigy		
Ardsley, NY	importer	none
2-Ethoxyethyl Acrylate		
Haven Chem.		
Philadelphia, PA	manufacturer	confidential
Sartomer Co.		
West Chester, PA	manufacturer	confidential
Alcolac		
Baltimore, MD	manufacturer	<1000

TABLE 1-2 (cont.)

Producer (location)	Source	Production Range (lbs)
2-Ethoxyethyl Methacrylate		
Sartomer Co. West Chester, PA	manufacturer	confidential
ICI Americas Wilminton, DE	importer	none
2-Ethoxyethyl Dodecanoate		
Schneid Inc. Atlanta, GA	manufacturer	confidential
Machemco Inc. Atlanta, GA	manufacturer	confidential
2-Ethoxyethanol, phosphated		
Arol Chem. Newark, NJ	manufacturer	1-10 thousand

2-Ethoxyethyl acrylate is manufactured by National Starch and Chemical Corp. in Salisbury, NC (SRI, 1984).

2-Ethoxyethyl acetate appears to be the only 2-ethoxyethanol ester produced in large industrial quantities. In 1983, 126.4 million pounds of 2-ethoxyethyl acetate were manufactured in the U.S. (USITC, 1984). Separate import and export data are not available from the U.S. Bureau of the Census.

The first step in the commercial production of 2-ethoxyethanol esters involves the alcoholysis of ethylene oxide to form mono-, di and triethers of ethylene glycol. The monoethyl ether is separated and used as an intermediate to produce the esters. For example, transesterification between the monoethyl ether and ethyl acetate yields 2-ethoxyethyl acetate and ethanol. 2-Ethoxyethyl acetate can also be made by esterifying the monoethyl ether with acetic acid (U.S. EPA, 1982a).

1.4. USE DATA

2-Ethoxyethyl acetate is industrially used as a blush retardant in lacquers; as a solvent for oils, nitrocellulose and resins; as a component of wood stains and varnish removers; and as an ingredient in products for the treatment of textiles and leather (U.S. EPA, 1982a). It is also used in the formulation of photoresist products by Eastman Kodak's Photographic Division (U.S. EPA, 1982b).

2-Ethoxyethyl acrylate is used as a monomer in the production of polymers and elastomers (Vial, 1979).

2-Ethoxyethyl dodecanoate is used as plasticizer (Hawley, 1977).

Phosphated 2-ethoxyethanol, is possibly used as a surface-active agent (cleaner) as Arol Chemical (the manufacturer listed in Table 1-2) manufactures these types of compounds (SRI, 1984).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

The fate of the 2-ethoxyethanol esters in the environment will depend upon the ability of the compounds to undergo biological, chemical and photochemical reactions and to transport or partition from one environmental matrix into another. Experimental data on the environmental fate mechanisms of the 2-ethoxyethanol esters are limited to only the acetate ester. The individual fate processes are discussed below with respect to water, air and soil. Fate estimations are projected from available physical properties where appropriate or necessary.

2.1. WATER

2.1.1. Microbial Degradation. Bridie et al. (1979a) determined the BOD, COD and ThOD of 2-ethoxyethyl acetate. The BOD tests were conducted in accordance with the standard dilution method at 20°C for a period of 5 days while the COD tests were conducted in accordance with the standard potassium dichromate method. The following results were obtained:

THOD	BOD		COD	
(g/g)	(g/g)	% of ThOD	(g/g)	% of ThOD
1.82	0.74	41	1.76	96

Price et al. (1974) conducted 20-day biodegradability tests on 2-ethoxyethyl acetate in nonacclimated freshwater and in nonacclimated seawater. Testing followed standard BOD procedures; seed material for the freshwater tests consisted of settled domestic wastewater while seed for the seawater tests was developed in seawater taken from Lavaca Bay, Texas. The biological oxidation of the 2-ethoxyethyl acetate (concentrations of 3, 7 or 10

ppm) for 5, 10, 15 and 20 days was 36, 79, 82 and 80%, respectively, in non-acclimated freshwater and 10, 44, 59 and 69%, respectively, in nonacclimated synthetic seawater.

The Japanese MITI test judges 2-ethoxyethyl acetate to be "well-biodegradable" since biodegradation as measured by oxygen consumption exceeded 30% after 2 weeks (Sasaki, 1978).

The standard protocol for this biodegradation test is described as follows (Sasaki, 1978):

1. Proportion of test substance to active sludge is usually 100 ppm to 30 ppm
2. Test temperature 25 $\pm$ 2°C
3. pH of the sludge supernatant 7.0 $\pm$ 1
4. Test period is 2 weeks
5. The percentage biodegradation from oxygen consumption is calculated as follows:

$$\text{Percentage biodegradation} = \frac{BOD-B}{TOD} \times 100$$

Where: BOD= biological oxygen demand (mg)

B: oxygen consumption of basal culture medium

TOD: Theoretical oxygen demand required when substance is completely oxidized.

6. The percentage biodegradation from results of direct analysis is calculated as follows:

$$\text{Percentage biodegradation} = \frac{Sb-Sa}{Sb} \times 100$$

Sa: Residual amount of test substance or total organic carbon after completion of the test

Sb: Residual amount of compound or organic carbon in the blank test with water to which only the test substance has been added.

2.1.2. Hydrolysis. Experimental environmental hydrolysis data were not found for 2-ethoxyethanol esters. U.S. EPA (1982a) reported that 2-ethoxyethyl acetate is not reactive with water; therefore, biodegradation is likely to be much more important than hydrolysis.

2.1.3. Oxidation. Pertinent data were not located in the available literature as cited in the Appendix.

2.1.4. Photolysis. Pertinent data were not located in the available literature as cited in the Appendix.

2.1.5. Transport.

2.1.5.1. VOLATILIZATION -- The water solubility (23 g/100 g) and vapor pressure (2 mm Hg) of 2-ethoxyethyl acetate at 20°C (see Section 1.2.) can be used to calculate a Henry's Law Constant of 1.5×10^{-6} atm-m³/mole. This value of Henry's Constant suggests that volatilization from environmental bodies of water will occur at a relatively slow rate (Lyman et al., 1982). Using a Henry's Constant of 1.5×10^{-6} atm-m³/mole, the U.S. EPA EXAMS Computer simulation (Burns et al., 1981) predicts the following volatilization half-lives in typical water bodies:

pond	306 days
river	169 days
oligotrophic lake	853 days
eutrophic lake	931 days

Vapor pressure data are not available for the other 2-ethoxyethanol esters; therefore, additional volatilization predictions cannot be made.

2.1.5.2. ADSORPTION -- The high water solubility and low octanol/water partition coefficient of 2-ethoxyethyl acetate suggest that adsorption by particulate matter and sediment are not likely to be important. The EXAMS simulation (Burns et al., 1981) predicts that virtually all of the compound will remain in the water column. Giusti et al. (1974) reported

that 2-ethoxyethyl acetate is adsorbed by activated carbon at a level of 0.132 g/g carbon.

2.1.5.3. **BIOACCUMULATION** -- Experimentally measured bioaccumulation data were not found for any of the 2-ethoxyethanol esters. The BCF of an organic compound may be estimated from its WS and K_{ow} by use of the following equations:

$$\text{Log BCF} = 0.76 \text{ Log } K_{ow} - 0.23 \quad \text{Veith et al., 1980} \quad (2\text{-}1)$$

$$\text{Log BCF} = 2.791 - 0.564 \text{ Log WS (in ppm)} \quad \text{Kenaga and Goring, 1978} \quad (2\text{-}2)$$

Using WS (23 g/100 g) and Log K_{ow} (0.710-see Section 1.2.), the BCFs for Equations 2-1 and 2-2 are calculated to be 2 and 0.6, respectively. These BCF values suggest that bioaccumulation of 2-ethoxyethyl acetate in aquatic organisms is not significant.

The WS of 2-ethoxyethyl acrylate is 5.5 weight % (Brown et al., 1980). Use of Equation 2-2 above predicts a BCF of 1.3. 2-Ethoxyethyl dodecanoate is reported as insoluble in water (Hawley, 1977), which suggests that it can potentially bioaccumulate to significant levels.

2.2. AIR

The photochemical reactivity of 2-ethoxyethyl acetate has been examined in smog chamber tests involving irradiation of the compound with nitrogen oxides (Farley, 1977; Yanaqihara et al., 1976, 1977). Reactivity was measured by measuring the depletion rate of NO, time to reach the maximum value for NO_2 and O_3, and HCHO and PAN yields. On the basis of maximum O_3 yield, 2-ethoxyethyl acetate was found to be moderately to highly reactive with a reactivity on the order of toluene.

An experimentally determined rate constant for the reaction of 2-ethoxyethyl acetate with hydroxyl radicals was not available. At 27°C, the hydroxyl radical rate constant with toluene, 1-propylacetate, and 2-butylacetate are 3.5, 2.7 and 3.4×10^{12} cm^3-mole/sec, respectively (Lyman et al., 1982). Assuming that the rate constant for 2-ethoxyethyl acetate is on the order of 10^{12} cm^3-mole/sec and that the OH concentration of an average atmosphere is 10^{-18} moles/cm^3, a half-life for 2-ethoxyethyl acetate of ~8 days can be calculated.

The relatively high water solubilities of 2-ethoxyethyl acetate and acrylate suggest that atmospheric removal by dissolution (rainfall) is possible.

2.3. SOIL

Fincher and Payne (1962) isolated bacteria from a soil that had been enriched for several days with aqueous solutions of triethylene glycol. In an aqueous mineral salts medium, the isolated bacteria were found to grow rapidly on 2-ethoxyethyl acetate.

Data pertaining to the chemical or photochemical degradation of the 2-ethoxyethanol esters in soil were not found.

The K_{oc} of an organic compound may be estimated from the WS or K_{ow} of the compound by use of the following equations:

$$\text{Log } K_{oc} = 3.64 - 0.55 \text{ Log WS (in ppm)} \quad \text{Kenaga and Goring, 1978} \qquad (2\text{-}3)$$

$$\text{Log } K_{oc} = 0.544 \text{ Log } K_{ow} + 1.377 \quad \text{Kenaga and Goring, 1978} \qquad (2\text{-}4)$$

For 2-ethoxyethyl acetate, the K_{oc} values calculated from Equations 2-3 and 2-4 are 5 and 58, respectively, indicating that 2-ethoxyethyl acetate is

expected to be highly mobile in soil. Use of Equation 2-3 predicts a K_{oc} value of ~11 for 2-ethoxyethyl acrylate.

Prediction of K_{oc} based on molecular topology and quantitative structure-activity relationship analysis (Sabljic, 1984) yield the following K_{oc} values:

2-ethoxyethyl acetate	629
2-ethoxyethyl acrylate	1,241
2-ethoxyethyl methacrylate	1,991
2-ethoxyethyl dodecanoate	370,550

The values predicted for 2-ethoxyethyl acetate and acrylate are significantly higher than prediction from WS. Higher K_{oc} values indicate a tighter adsorption to the organic content in soil. The insolubility of 2-ethoxyethyl dodecanoate in water predicts immobility in soil as does the K_{oc} value above.

The evaporation rate for 2-ethoxyethyl acetate at 77°F, 0-5% relative humidity and an airflow of 21 ℓ/minute from a nonadsorbing surface is 50% evaporated in 25 minutes (Davis, 1966). Therefore, evaporation from dry soil surfaces is likely to be important in the absence of significant soil adsorption. Evaporation from moist soils is difficult to predict without experimental data.

2.4. SUMMARY

2-Ethoxyethyl acetate appears susceptible to significant microbial degradation in both soil and aquatic environments. There is no data available to indicate that chemical removal mechanisms, other than microbial, are important in either soil or aquatic media.

Estimation methods predict that bioaccumulation of 2-ethoxyethyl acetate or acrylate in aquatic organisms is not significant. 2-Ethoxyethyl acetate

is expected to volatilize slowly, at a relatively insignificant rate, from aquatic environments.

In the atmosphere, 2-ethoxyethyl acetate may be removed chemically with an estimated half-life of 8 days by reaction with hydroxyl radicals. Its high water solubility suggests that physical removal by dissolution (rainfall) is possible.

In soil, sorption coefficient estimation from water solubility predict that 2-ethoxyethyl acetate and acrylate will be highly mobile and will be susceptible to significant leaching; however, estimation from molecular topology and quantitative structure-activity relationship analysis predict a much tighter binding of the compounds to organic materials in soil. Experimental leaching tests are required to determine actual mobility.

3. EXPOSURE

3.1. WATER

The U.S. EPA STORET Data Base contained no observations with respect to the 2-ethoxyethanol esters. Other aquatic monitoring data were not encountered.

Exposure of the 2-ethoxyethanol esters to the aquatic environment appears most likely from their industrial producton and use. Rainwater may contain 2-ethoxyethyl acetate as a result of dissolution of vapor-phase exposures of the compound to the atmosphere.

3.2. FOOD

Pertinent data regarding exposure of the 2-ethoxyethanol esters in food were not located in the available literature as cited in the Appendix.

3.3. INHALATION

Exposure of 2-ethoxyethyl acetate to the air appears most significant from its use as a solvent in paints, varnishes and stains. For example, application of paint to a surface results in the evaporation of the solvents into the air. The estimated emission rate of 2-ethoxyethyl acetate into the atmosphere from painting operations at the General Motors automotive assembly plant in Janesville, Wisconsin has been reported to be 37.9 gallons/hour (Sexton and Westberg, 1980).

Clapp et al. (1984) reported 2-ethoxyethyl acetate concentrations of 0-1.2 ppm within a chemical plant engaged in the redistribution of the compound. 2-Ethoxyethyl acetate has also been occupationally monitored in other facilities using the compound (Boiano, 1983; Gilles, 1977; Hamlin et al., 1982). Monitoring data regarding general ambient atmospheric concentrations of the 2-ethoxyethanol esters were not found, but occupational exposure to 2-ethoxyethanol acetate may be significant (U.S. EPA, 1982a).

3.4. DERMAL

Pertinent monitoring data were not located in the available literature as cited in the Appendix.

4. PHARMACOKINETICS

This chapter will discuss the pharmacokinetics of 2-ethoxyethanol acetate only. Pertinent data regarding other 2-ethoxyethanol esters were not located in the available literature as cited in the Appendix.

4.1. ABSORPTION

Limited direct evidence concerning the absorption of 2-ethoxyethanol acetate is available. Dugard et al. (1984) used isolated human abdominal epidermis to demonstrate that 2-ethoxyethanol acetate is readily absorbed with an absorption rate of 0.800 mg/cm²/hr. This is comparable with the rate for 2-ethoxyethanol (0.796 mg/cm²/hr). A similar result was obtained by Guest et al. (1984) by applying (ethyl-1,2-^{14}C) 2-ethoxyethanol acetate to the thorax of beagle dogs for 60 minutes and measuring the amount of radioactivity in urine over a 24-hour period. A rate of 110 nmol/cm²/min (0.868 mg/cm²/hr) was calculated, a value analogous to those obtained for other lipid-soluble compounds. In vitro percutaneous absorption of 2-ethoxyethanol acetate using beagle thorax skin yielded a somewhat higher rate of absorption, 292 nmol/cm²/min (2.3 mg/cm²/hr). Guest et al. (1984) also examined inhalation exposures and demonstrated rapid pulmonary absorption of 2-ethoxyethanol acetate. After 10 minutes, absorption was ~80% (as inferred from the concentration of 2-ethoxyethanol acetate in the expired air) and leveled off at 68% at 3 hours.

Although additional data concerning absorption of 2-ethoxyethanol acetate are unavailable, it is apparent from toxicological studies (see Chapter 5) that 2-ethoxyethanol acetate is effectively absorbed orally, dermally and by inhalation.

4.2. DISTRIBUTION

Intravenous administration of ^{14}C-2-ethoxyethanol acetate to beagle dogs led to an elimination half-life from the blood of 7.9 hours. Also indicative of rapid clearance from the blood was the swift decline in post-exposure 2-ethoxyethanol acetate breath concentration in dogs (Guest et al., 1984). There is no evidence to show the active uptake of 2-ethoxyethanol acetate by those organs most susceptible to its toxic effects.

4.3. METABOLISM

2-Ethoxyethanol acetate is generally believed to undergo acetate hydrolysis to 2-ethoxyethanol by the ubiquitous esterases (U.S. EPA, 1982a). Miller et al. (1984) provided indirect evidence for hydrolysis of 2-ethoxyethanol acetate to 2-ethoxyethanol by demonstrating that propylene glycol monomethyl ether acetate is metabolized to the parent glycol ether. An *in vitro* study using rat plasma revealed that the half-life of 2-ethoxyethanol acetate as measured by gas-liquid chromatography is ~10 minutes (Hoffman, 1984). These data in conjunction with toxicological studies that report similar effects produced by 2-ethoxyethanol and 2-ethoxyethanol acetate at similar doses (on a mole/kg basis) support the involvement of ester hydrolysis in 2-ethoxyethanol acetate metabolism.

If 2-ethoxyethanol is the product of 2-ethoxyethanol acetate hydrolysis, then further metabolism may result in the formation of ethoxyacetic acid and its glycine conjugate, the major urinary metabolites from rats administered 2-ethoxyethanol orally or by inhalation (Cheever et al., 1984; Jonsson et al., 1982). Other metabolites include CO_2 and several unidentified urinary products, which combined represent no more than 15% of the administered dose (Cheever et al., 1984; Jonsson et al., 1982). The only study

involving 2-ethoxyethanol acetate reported that trace amounts of radioactivity as CO_2 and volatile organics were detected in the breath of dogs receiving ^{14}C-2-ethoxyethanol acetate intravenously or percutaneously (Guest et al., 1984).

4.4. EXCRETION

The only study pertaining to 2-ethoxyethanol excretion was performed by Guest et al. (1984) and involved the recovery of radioactivity in dogs following intravenous and percutaneous administration of (ethyl-1,2-^{14}C-2-ethoxyethanol. Approximately 61% of the radioactivity was excreted in the urine 24 hours following intravenous administration of 1 mg/kg ^{14}C-2-ethoxyethanol. Less than 1% of the dose was recovered as CO_2 and volatile organics within 8 hours of intravenous dosing. Urinary radioactivity was detected in dogs percutaneously exposed to 2-ethoxyethanol acetate in a pattern similar to that observed after intravenous administration, although the percent recovery was not given. Measurements of radioactivity in feces or carcasses were not performed, nor was identification of the urinary products.

5. EFFECTS

This chapter will discuss the effects of 2-ethoxyethanol acetate only. Pertinent data regarding other 2-ethoxyethanol esters were not located in the available literature as cited in the Appendix.

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of 2-ethoxyethanol acetate were not located in the available literature as cited in the Appendix, and this chemical is not scheduled for testing by NTP (1984).

5.2. MUTAGENICITY

Pertinent data regarding the mutagenicity of 2-ethoxyethanol acetate were not located in the available literature as cited in the Appendix.

5.3. TERATOGENICITY

Three inhalation studies and one dermal study have established 2-ethoxyethanol acetate as a teratogenic and fetotoxic agent in both rats and rabbits (Table 5-1). Hardin et al. (1984) administered 0.35 mL (343 mg) 2-ethoxyethanol acetate 4 times/day to the backs of 18 pregnant Sprague-Dawley rats during gestation days 7-16. The dams had significant decreases in body weight gain that were probably due to decreases in gravid uterus weights, but showed no other signs of maternal toxicity. Embryotoxicity was strongly indicated as evidenced by significant increases in the number of totally resorbed litters and in the number of dead implants per litter and significant decreases in the number of live fetuses per litter and in fetal body weight. Additionally, the incidences of skeletal variations and cardiac malformations were higher than water-treated controls thus implicating 2-ethoxyethanol acetate as a teratogen.

TABLE 5-1

Teratogenicity and Fetotoxicity of 2-Ethoxyethanol Acetate

Route	Species/Strain	Dose/Exposure	Maternal Response	Progeny Response	Reference
Inhalation	NZW rabbits	50 ppm (270 mg/m³) 6 hours/day gestation days 6-18	None	None	Union Carbide, 1984
		100 ppm (541 mg/m³) 6 hours/day gestation days 6-18	Altered hematologic profile; decreased food consumption	Decreased ossification	Union Carbide, 1984
		200 ppm (1081 mg/m³) 6 hours/day gestation days 6-18	Altered hematologic profile; decreased food consumption; decreased weight gain; occult blood; hematuria; decreased gravid uterine weight	Decreased ossification; increased incidence of totally resorbed litters; decreased number of viable implants or live fetuses per litter; increased visceral, skeletal, external malformations; increased number nonviable implants	Union Carbide, 1984
		300 ppm (1622 mg/m³) 6 hours/day gestation days 6-18	Same as above plus increased absolute liver weight	Increased total resorbed litters; increases nonviable implants or live fetuses/litter; increased visceral, skeletal, external malformations; 100% total malformations; increased nonviable implants; decreased ossification	Union Carbide, 1984
Inhalation	rat/Fischer 344	50 ppm (270 mg/m³) 6 hours/day gestation days 6-15	Increased absolute liver weight	None	Union Carbide, 1984
		100 ppm (541 mg/m³) 6 hours/day gestation days 6-15	Altered hematologic profile; increased absolute and relative liver weight	Increased incidence of visceral, skeletal variants	Union Carbide, 1984
		200 ppm (1081 mg/m³) 6 hours/day gestation days 6-15	Same as above plus: decreased weight gain; decreased food consumption	Same as above plus: decreased fetal body weight; increased incidence of visceral, skeletal and total malformations	Union Carbide, 1984

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TABLE 5-1 (cont.)

Route	Species/Strain	Dose/Exposure	Maternal Response	Progeny Response	Reference
Inhalation	rat/Fischer 344	300 ppm (1622 mg/m³) 6 hours/day gestation days 6-15	Altered hematologic profile; increased absolute and relative liver weight; decreased weight gain; decreased food consumption	Increased incidence of visceral, skeletal variants; decreased fetal body weight; increased incidence of visceral, skeletal and total malformations; increased incidence external variants; increased nonviable implants/litter	Union Carbide, 1984
Inhalation	rabbit/Dutch	25 ppm (135 mg/m³) 6 hours/day gestation days 6-18	None	One fetus had missing left kidney	Doe, 1984
		100 ppm (541 mg/m³) 6 hours/day gestation days 6-18	None	Decreased fetal weight; one fetus had misplaced ovary; one fetus had malrotated forelimb; increased minor skeletal defects	Doe, 1984
		400 ppm (2162 mg/m³) 6 hours/day gestation days 6-18	Decreased weight gain; decreased food consumption altered hematologic profile	Increased intrauterine death; decreased fetal weight; moreased external, visceral variants; increased skeletal varisnts and malformation	Doe, 1984
Inhalation	rat/SD	130 ppm (703 mg/m³) 7 hours/day gestation days 7-15	None	Decreased fetal weight; one fetus had heart defect; increased skeletal variants	Nelson et al., 1984
		390 ppm (2108 mg/m³) 7 hours/day gestation days 7-15	Weight reduction	Increased resorptions/litter; decreased fetal weight; increased visceral and skeletal variations and malformations	Nelson et al., 1984
		600 ppm (3243 mg/m³) 7 hours/day gestation days 7-15	Weight reduction	100% resorptions	Nelson et al., 1984
Dermal	rat/SPF SD	0.35 ml 4 times/day gestation days 7-16	Decreased weight gain; decreased gravid uterus weight	Increased incidence completely resorbed litters; increased number live fetuses/litter, decreased fetal body weight; increased incidences of skeletal variations and cardiac malformations	Hardin et al., 1984

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Groups of 9-15 pregnant Sprague-Dawley rats were exposed to atmospheres containing 130, 390 or 600 ppm (703, 2108 or 3243 mg/m³) 2-ethoxyethanol acetate, 7 hours/day during days 7-15 of gestation in a study by Nelson et al. (1984). Other than an unspecified weight reduction at the higher concentrations, no signs of maternal toxicity were noted. At 600 ppm, all litters were totally resorbed while the 390 ppm group had a significant increase in resorptions per litter. Live fetal weights were significantly depressed in the low and medium-dose groups. The incidence of visceral malformations was higher in the 390 ppm treated rats mostly because of cardiovascular defects. One fetus from the low-dose dams had a ringed aortic arch, which was considered a teratogenic rather than a spontaneous defect. Skeletal malformations (ribs) and visceral variations (cardiovascular and urogenital) were more frequent in fetuses from 390 ppm exposed dams, while both the 130 and 390 ppm groups had higher incidences of skeletal variations compared with controls. These data demonstrate that in the rat 130 ppm 7 hours/day is close to the teratogenic threshold, while 390 and 600 ppm 7 hours/day are clearly teratogenic and fetotoxic.

Doe (1984) exposed groups of 15-19 Dutch rabbits by inhalation to 25, 100 and 400 ppm (135, 541 and 2162 mg/m³) of 2-ethoxyethanol acetate, 6 hours/day during gestation days 6-18. At a level of 25 ppm the only defect reported that occurred in one fetus was agenesis of the left kidney. Mean fetal weight was significantly depressed in fetuses from 100 ppm exposed doses. In addition, this group had an enhanced frequency of skeletal variants as well as one fetus with an ovary attached to the intestine and another with a malrotated forelimb. The high-dose group (400 ppm) had concomitant decreases in food consumption and weight gain as well as a reduced hemoglobin concentration and nonsignificant alterations in

unspecified erthrocyte parameters. There was a higher rate of postimplantation loss, a decrease in live fetuses per litter and depressed mean live fetal weight at 400 ppm. Fetuses in this exposure group had statistically significant incidences of external and visceral variations (pelvic dilation splecn, opaque/empty gall bladders, pale and reduced spleens), skeletal variations (reduced ossification), and skeletal malformation (multiple vertebral defects). These data reveal a teratogenic level of 400 ppm, 6 hours/day, and a fetotoxic level of 100 ppm 6 hours/day in rabbits.

Exposure to 2-ethoxyethanol acetate at concentrations of 50, 100, 200 or 300 ppm (270, 541, 1081 or 1622 mg/m^3), 6 hours/day in groups of 24 New Zealand rabbits (gestation days 6-18) and groups of 30 Fischer 344 rats (gestation days 6-15) was performed in a recent study by Union Carbide (1984). No effects were observed in either species at 50 ppm except for an increase in absolute liver weight in pregnant rats. At 100 ppm in rabbits, decreased food consumption and an altered hematologic profile were observed in the dams, while the fetuses exhibited decreased ossification. Maternal effects in the 200 ppm group included those seen at 100 ppm as well as decreased weight gain, occult blood, hematuria, and depressed gravid uterine weight. Litter data from this group revealed an increase in the number of total resorptions, a decrease in the number of viable implants per litter and a significant rise in the number of visceral, skeletal and external malformations. A dose-response relationship was further strengthened by results from the high-dose treatment group. Dams exhibited similar signs to those seen in lower exposure groups with the addition of an increase in absolute liver weight. Fetal effects were similar in variety to the 200 ppm group but more severe as demonstrated by a 100% incidence of major cardiovascular and renal malformations.

The pattern and dose-response of effects in rat dams and offspring were similar to those in rabbits (Union Carbide, 1984). Maternal responses included altered hematologic parameters and increased absolute and relative liver weights at 100, 200 and 300 ppm, while decreases in food consumption and weight gain were noted at the two higher exposures. Rat fetuses experienced increased visceral and skeletal variations at 100 ppm. Similar effects plus decreased body weight and visceral and skeletal malformations occurred at 200 ppm. At 300 ppm, similar, as well as increased, incidences of external variations and number of nonviable implants per litter were observed. These data indicate that ethoxyethanol acetate is fetotoxic at 100 ppm, 6 hours/day, teratogenic at 200 ppm, 6 hours/day, and has no effect at 50 ppm, 6 hours/day.

5.4. OTHER REPRODUCTIVE EFFECTS

The data concerning the reproductive effects of 2-ethoxyethanol acetate exclusive of teratogenicity and fetotoxicity are quite limited. The Union Carbide (1984) study (see Section 5.3.) reported no effects on pregnancy rate in rats and rabbits exposed during gestation to 50-300 ppm (270-1622 mg/m^3), 6 hours/day 2-ethoxyethanol acetate. In a footnote to the Nelson et al. (1984) teratogenicity study, small groups of rats were exposed to 130, 390, or 600 ppm (703, 2108 or 3243 mg/m^3) on gestation days 14-20 (exposures are assumed to be 7 hours/day as in the main study although this is not explicitly stated). The high and medium doses extended pregnancy by 24 and 12 hours, respectively, while the 130 ppm group had a normal gestation period.

Nagano et al. (1979, 1984) investigated the testicular effects in JCR-ICR mice of 2-ethoxyethanol acetate administered orally 5 days/week for 5 weeks at doses ranging from 500-4000 mg/kg. A dose-related decrease in

testicular weight was observed in mice given 1000-4000 mg/kg. These mice also exhibited testicular atrophy in the form of seminiferous epithelium degeneration. The lowest dose (500 mg/kg) had no effect.

Truhaut et al. (1979) reported no adverse testicular effects in rats and rabbits exposed to 200 ppm (1081 mg/m³) 2-ethoxyethanol acetate 4 hours/day, 5 days/week for 10 months.

5.5. SUBCHRONIC AND CHRONIC TOXICITY

Nagano et al. (1979, 1984) administered 2-ethoxyethanol acetate at dosages of 0, 500, 1000, 2000 or 4000 mg/kg/day by gastric intubation 5 days/week for 5 weeks to groups of five male JCL-ICR mice; a significant decrease was observed in white cell count at 2000 and 40000 mg/kg/day and a reduction in packed cell volume at 4000 mg/kg/day. At 1000-4000 mg/kg/day, there was a dose-related decrease in relative testicular weight and degeneration of the seminiferous epithelium. Histologic examination was limited to the testis. No effects were observed at 500 mg/kg/day.

Dogs (3 adults) inhaling 600 ppm (3243 mg/m³) 2-ethoxyethanol acetate, 7 hours/day, 5 days/week for 24 weeks had no detrimental effects on weight gain or blood and clinical parameters nor were any gross or microscopic lesions found in any organs (Carpenter, 1947)

The only study involving chronic 2-ethoxyethanol acetate exposures was performed by Truhaut et al. (1979) who exposed groups of 10 male or 10 female Wistar rats and groups of 2 male and 2 female New Zealand rabbits to 200 ppm (1081 mg/m³), 4 hours/day, 5 days/week for 10 months. Gross and histologic examination of major organs was performed. Although no differences in body weight or hematological parameters or urinalysis were observed compared with matched controls, histopathological examination revealed focal tubular nephritis with epithelial degeneration in rabbits and male rats.

These lesions did not occur in controls. Incidences or severity of the lesions were not reported.

5.6. OTHER RELEVANT INFORMATION

The acute effects of 2-ethoxyethanol acetate in a number of species are summarized in Table 5-2. Acute exposure to 2-ethoxyethanol acetate in animals can result in vomiting, cramps, narcoses, paralysis and albuminuria. Primary effects involve injury to the CNS, kidneys and lungs (Browning, 1965). Hemoglobinuria or hematuria or both were observed in rats and rabbits exposed orally, percutaneously or by inhalation in the acute toxicity experiments conducted by Truhaut et al. (1979). Ketonuria was evident in these animals after oral and dermal exposure as was blood in the kidneys and bladder, while a transient decrease in white cell count (up to 70%) was noted in rabbits following percutaneous absorption. Histopathologic examination revealed acute glomerulo-tubular nephrosis in rats exposed orally while rabbits exhibited renal inflammation following dermal exposure. Carpenter (1947) reported that rats exposed to 1500 ppm (8845 mg/m^3) 2-ethoxyethanol acetate for 4 hours exhibited no signs of methemoglobinemia nor did dogs 2 hours after receiving 1000 mg/kg 2-ethoxyethanol acetate orally. These same dogs were exposed to 1000 ppm (5405 mg/m^3) 2-ethoxyethanol acetate vapor for 4 hours the following day and again negative results were obtained. However, one of the dogs was severely incapacitated by the exposure and displayed anorexia, burned corneas, bloody diarrhea and liver damage as indicated by impaired sulfobromophthalein retention. The author concluded that 2-ethoxyethanol is similar in toxicity to methyl ethyl ketone, propylene dichloride and tetrachloroethylene, although the hazard posed by 2-ethoxyethanol acetate may be substantially less because of its appreciably lower vapor pressure.

TABLE 5-2

Acute Effects of 2-Ethoxyethanol Acetate

Route	Species	Dose (g/kg)	Response	Reference
Oral	rat (male)	5.10	LD_{50} (14 day)	Carpenter, 1947
	rabbit (male)	1.95	LD_{50} (14 day)	Carpenter, 1947
	guinea pig (male)	1.91	LD_{50} (14 day)	Carpenter, 1947
Dermal	guinea pig	18.8	LD_{50}	Carpenter, 1947
	rabbit (male)	10.3	LD_{50}	Carpenter, 1947
Inhalation	rat (male)	1500 ppm (8108 mg/m³), 8 hours	2/6 died	Carpenter, 1947
	rat	3000 ppm (16,216 mg/m³), 4 hours	LC_{LO}	Nelson et al., 1984
Oral	rat (male)	3.9	LD_{50}	Truhaut et al., 1979
	rat (female)	2.9	LD_{50}	Truhaut et al., 1979
Dermal	rabbit	10.5	LD_{50}	Truhaut et al., 1979
Inhalation	rat	>2000 ppm (10,811 mg/m³), 4 hours	LC_{50}	Truhaut et al., 1979
	rabbit	>2000 ppm (10,811 mg/m³), 4 hours	LC_{50}	Truhaut et al., 1979

2-Ethoxyethanol acetate is considered irritating to eyes and skin only at high concentrations or when exposure is prolonged or frequent (Rowe and Wolf, 1982; Tennessee Eastman, 1982). There are no recorded instances of human exposure to 2-ethoxyethanol acetate by itself, possibly because the concentration at which vapors are intolerable is below the toxic level.

Cohen and Maier (1973) reported that workers exposed to an epoxy resin paint containing 2-ethoxyethanol acetate (exposure measured as 9.4-442 mg/m^3) along with Stoddand solvent and toluene experienced nausea, burning eyes, dryness of nose and throat, headache, dizziness and insomnia. Whether these symptoms were wholly or in part due to 2-ethoxyethanol acetate could not be determined.

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

Few data on the effects of 2-ethoxyethanol esters on aquatic organisms were located in the available literature. Bridie et al. (1979b) investigated the 24-hour acute toxicity of 2-ethoxyethanol acetate to the goldfish, Carassius auratus, using a standardized static nonrenewal procedure maintained at 20±1°C. The LC_{50} of 160 mg/ℓ was reported. A 24-hour median tolerance limit of 4000 mg/ℓ ethoxyethanol acetate to brine shrimp, Artemia salina, endpoint mortality, was determined in a preliminary investigation by Price et al. (1974).

Holcombe et al. (1984) determined the 96-hour LC_{50} of 2-ethoxyethanol acetate to fathead minnows, Pimephales promelas, channel catfish, Ictalurus punctatus, and snails, Aplexa hypnorum. All tests were conducted using modified proportional diluters with dilution factors of 0.6. Water for all tests was obtained from Lake Superior and was maintained at 24.6±1.4°C. Concentrations of the toxicant were supplied at the rate of 100 mℓ/minute to randomized duplicate tanks of five exposure concentrations plus a control. Mean measured exposure concentrations, monitored daily throughout the test period, were 0.0 (control), 13.5, 21.6, 31.4, 60.3, and 107 ppm 2-ethoxyethylacetate. Dissolved oxygen, hardness, alkalinity and pH were monitored throughout the test and means reported as 7.4 ppm, 44.9 mg/ℓ, 42 9 mg/ℓ and 6.9-7.7, respectively. The glass exposure tanks, yielding a volume of 7.3 ℓ, were held under a constant 16-hour photoperiod.

Fifty fathead minnows (average weight 134 mg; 31-35 days after hatch) and 20 channel catfish (average weight 3.4 g) and adult snails, evenly distributed between duplicate tanks, were exposed in each concentration and in controls. Snails were counted into enclosed stainless steel screen

cylinders 10x3 cm wide. The cylinders were then randomly distributed into exposure tanks containing fathead minnows. Mortality from the duplicate exposure tanks were pooled before calculations of the LC_{50}s.

The LC_{50} values for fathead minnows, channel catfish and snails is presented in Table 6-1. Species sensitivity factors were derived by dividing the 96-hour LC_{50} value of the least sensitive species by the 96-hour LC_{50} for the most sensitive species. Channel catfish (96-hour LC_{50}, 44.8 mg/ℓ) were ~1.1 times less sensitive than fathead minnows (96-hour LC_{50}, 42.2 mg/ℓ) to ethoxyethanol acetate. Snails (96-hour LC_{50}, 65.2 mg/ℓ) were 1.5 times less sensitive than fathead minnows to 2-ethocyethyl acetate.

In the discussion, Holcombe et al. (1984) compared the 96-hour LC_{50} value of fathead minnow of 42.2 mg/ℓ ethoxyethanol acetate with the 96-hour LC_{50} value of 45.0 mg/ℓ ethoxyethanol acetate to bluegill reported by Dawson et al. (1977) and concluded that bluegills appear to be somewhat more sensitive than fathead minnows. However, upon evaluation of the publication of Dawson et al. (1977) the compound tested was actually 2-methoxyethanol acetate and not 2-ethoxyethanol acetate.

6.2. CHRONIC EFFECTS

Johnson et al. (1984) investigated the toxicological effects of 2-ethoxyethanol acetate on adult and developing hydra, Hydra attenata. Approximately 700-1000 adult hydra were collected and dissociated mechanically into their component cells. The cells were then randomly reassociated into gently packed small pellets through low-speed centrifugation. Such reaggregated cells undergo a full ontogenesis sequence within 92 hours, giving rise to a new population of adult polyps.

TABLE 6-1

The 24-, 48-, 72- and 96-hour LC_{50} Values (mg/ℓ) for Various Species Exposed to 2-Ethoxyethyl Acetate[a]

Species	24-Hour LC_{50}	48-Hour LC_{50}	72-Hour LC_{50}	96-Hour LC_{50}
Fathead minnow *Pimephales promelas*	44.0 (43.0-45.1)[b]	43.5 (3.14-60.3)[c]	42.6 (41.4-43.8)	42.2 (40.7-43.6)
Channel catfish *Ictalurus punctatus*	80.1 (60.3-107)[c]	60.9 (53.1-69.7)	44.8 (42.2-47.6)	44.8 (42.2-47.6)
Snails[d]	--	--	--	65.2 (57.0-74.5)

[a]Source: Holcombe et al., 1984

[b]LC_{50} values and their respective 95% confidence intervals

[c]Confidence intervals (>99.9%) were calculated for these time periods using a binomial test.

[d]Only 96-hour mortality counts were made with snails.

The MEC of 0.6 mL/L 2-ethoxyethanol acetate was determined to be the same for both the adult and the developing hydra. Hence, the effect of 2-ethoxyethanol acetate on the hydra was reported to be coeffective (i.e., exhibiting no propensity for injury to one life stage versus another) (Johnson et al., 1984). Although the duration of exposure was not reported for either the adult or developing hydra, the exposure may have occurred throughout the 92-hour ontogenesis sequence.

6.3. PLANT EFFECTS

Pertinent data regarding the effects of 2-ethoxyethanol esters on aquatic plants were not located in the available literature as cited in the Appendix.

6.4. RESIDUE

Pertinent data regarding 2-ethoxyethanol ester residues in aquatic organisms were not located in the available literature as cited in the Appendix.

6.5. OTHER RELEVANT INFORMATION

Additional data regarding the toxic effects of 2-ethoxyethanol esters were not located in the available literature as cited in the Appendix.

7. GUIDELINES AND STANDARDS

7.1. HUMAN

ACGIH (1980, 1984) recently adopted a revised TLV for 2-ethoxyethanol esters of 5 ppm (27 mg/m³), which is analagous to that recommended for 2-ethoxyethanol. This is reasonable since the two compounds have been shown to exert similar effects at similar molar concentrations. OSHA has established a permissable exposure limit (PEL) of 100 ppm (540 mg/m³), which is actually 2-fold lower than that for 2-ethoxyethanol (CFR, 1981). Both of these recommendations are accompanied by the "skin" notation indicating that dermal absorption is a potentially hazardous route of exposure.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of 2-ethoxyethanol esters were not located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

This chapter will only discuss 2-ethoxyethanol acetate since pertinent data regarding other 2-ethoxyethanol esters were not located in the available literature as cited in the Appendix.

No data concerning the carcinogenicity or mutagenicity of 2-ethoxyethanol acetate were available. Furthermore, 2-year studies using rats exposed to 2-ethoxyethanol, the putative metabolite of 2-ethoxyethanol acetate, have been negative regarding increased tumor incidences (Morris et al., 1942; Melnick, 1984).

Short-term studies have indicated that 2-ethoxyethanol acetate exerts effects on the fetus, testis, and blood. Union Carbide (1984) reported that inhalation exposures ranging from 100-300 ppm (541-1622 mg/m^3) 6 hours/day during organogenesis resulted in a number of fetal and maternal effects in rats and rabbits (see Table 5-1). Dose-related alterations in hematologic parameters and decreases in food consumption and weight gain were generally obse.ved in the pregnant animals. Fetal effects also appeared to be dose-related; therefore, 2-ethoxyethanol acetate can be classified as embryotoxic (i.e., increased resorptions), fetotoxic (increased incidence of variants or minor defects), and teratogenic (increased incidence of visceral and skeletal malformations). A level of 50 ppm (270 mg/m^3), 6 hours/day had no effect on dams and offspring in both species.

By expanding the exposure level of 270 mg/m^3 over a 24-hour day, multiplying by the rat inhalation rate (0.223 m^3/day) and the absorption coefficient (estimated to be 0.7 from data presented in Section 4.1.) and dividing by the rat body weight (0.35 kg), an equivalent oral dose of 30.1 mg/kg/day can be calculated for rats. An equivalent oral dose for rabbits

of 24.9 mg/kg/day can be calculated similarly by assuming a rabbit inhalation rate of 2.0 m^3/day and a body weight of 3.8 kg (U.S. EPA, 1985). The next higher exposure level of 541 mg/m^3, 6 hours/day at which fetotoxicity was observed, is equivalent to oral doses of 60.3 and 49.8 mg/kg/day for rats and rabbits, respectively.

A similar exposure protocol was used by Doe (1984) who exposed pregnant rabbits to 25, 100 or 400 ppm (135, 541 or 2162 mg/m^3) 2-ethoxyethanol acetate, 6 hours/day during days 6-18 of gestation. Fetotoxicity as evidenced by depressed fetal weights and minor skeletal defects was reported at the two higher doses. Teratogenicity and maternal toxicity were indicated only at 400 ppm (2162 mg/m^3) by increased skeletal malformations in the fetuses and decreased weight gain, food consumption and altered hemograms in the dams. The low-dose group (135 mg/m^3, 6 hours/day) exhibited no effects (one fetus with kidney agenesis was not considered significant). This exposure level is equivalent to an oral dose of 12.5 mg/kg/day, using the same assumptions as above.

The preceding two studies were supported by another inhalation study of rats exposed to 130. 390 or 600 ppm (703, 2108 or 3243 mg/m^3) 2-ethoxyethanol acetate, 7 hours/day on days 7-15 of gestation (Nelson et al., 1984). The low-dose group exhibited signs of fetotoxicity (decreased fetal weight and increased skeletal variants), while the middle-dose group had increased incidences of major visceral and skeletal malformations. The 600 ppm (3242 mg/m^3) exposed rats experienced total resorptions. The lowest exposure level in this study is equivalent to an oral dose of 91.4 mg/kg/day.

One other study investigating the teratogenic potential of 2-ethoxyethanol acetate used dermal exposure. Hardin et al. (1984) observed that 0.35 ml (~343 mg) applied to the backs of pregnant rats 4 times daily during gestation days 7-16 resulted in increased intrauterine death.

Although this study is not useful for risk assessment, it is important in demonstrating that dermal absorption, a relevant route of exposure in the workplace, can result in effects similar to those seen following inhalation.

Rats and rabbits exposed by inhalation to 2-ethoxyethanol acetate at 200 ppm (1081 mg/m³), 4 hours/day, 5 days/week for 10 months had focal tubular nephritis and degeneration of the tubule epithelium (Truhaut et al., 1979). Expanding this exposure over a 24-hour day and 7-day week, (using the same assumptions for calculating an oral dose from inhalation exposures) results in doses of 57.4 mg/kg/day for rats and 47.5 mg/kg/day for rabbits.

No effects were observed in dogs exposed to 600 ppm (3243 mg/m³), 7 hours/day, 5 days/week for 24 weeks (Carpenter, 1947). This exposure is equivalent to 159.6 mg/kg/day, assuming an inhalation rate of 4.3 m³/day and a body weight of 12.7 kg for dogs (U.S. EPA, 1985).

The only oral study pertaining directly to the effects of 2-ethoxyethanol acetate was by Nagano et al. (1979, 1984) who exposed mice to 500, 1000, 2000 or 4000 mg/kg/day, 5 days/week for 5 weeks. A dose-related increase in testicular atrophy was noted starting at 1000 mg/kg/day while the two higher doses resulted in depressed white cell counts. No effects were observed at 500 mg/kg/day, 5 days/week (357 mg/kg/day). Although this is the only study of repeated oral exposure to 2-ethoxyethanol acetate, it is inappropriate to derive an ADI from these data for several reasons: other endpoints were not investigated adequately; the short duration of the study limits its usefulness for risk assessment; and fetotoxic and teratogenic effects were observed at equivalent oral doses that are ~10-fold lower than 357 mg/kg/day.

Although the data concerning the adverse effects of 2-ethoxyethanol acetate are somewhat limited, they appear to be sufficient to establish the fetus as being most susceptible to 2-ethoxyethanol acetate exposure. NOELs of 30.1 mg/kg/day for rats and 24.9 and 12.5 mg/kg/day for rabbits and a LOAEL of 49.8 mg/kg/day for rabbits have been established. 2-Ethoxyethanol acetate is believed to undergo hydrolysis to 2-ethoxyethanol. Inhalation teratology data for 2-ethoxyethanol agree well with the data presented for the acetate. Doe (1984) exposed groups of pregnant rats to 0, 10, 50 or 250 ppm 2-ethoxyethanol 6 hours/day on days 6-15 of gestation. No effects were observed in the 10 ppm group which received an estimated dose of 6 mg/kg. The 50 ppm group (30.1 mg/kg) showed evidence of fetotoxicity characterized by retarded skeletal ossification. On a molecular weight basis these doses correspond to 8.9 and 44.3 mg/kg 2-ethoxyethanol acetate for the NOEL and LOAEL, respectively. These doses are in good agreement with the NOEL of 30.1 mg/kg and the LOAEL of 49.8 mg/kg determined using 2-ethoxyethanol acetate.

The only oral study of 2-ethoxyethanol acetate (Nagano et al., 1979, 1984) also supports the comparable toxicity of 2-ethoxyethanol and 2-ethoxyethanol acetate. In these studies a NOEL of 357 mg/kg was determined for both compounds for testicular atrophy following 5 days of exposure.

Because of the inherent uncertainties in the estimation of oral equivalent doses from inhalation studies, especially intermittent inhalation studies, it is preferable when possible to base oral ADI estimates on oral data. Melnick (1984) administered 0, 500, 1000 or 2000 mg/kg bw 2-ethoxyethanol by gavage to rats and mice 5 days/week for 103 weeks (TWA doses 0, 357, 714 and 1429 mg/kg/day). In mice 357 mg/kg bw/day represented a NOEL, while in rats 357 mg/kg bw/day represented a LOAEL characterized by reduced body weights in males and females as well as adrenal enlargement in males.

In contrast, an oral teratology study (Stenger et al., 1971) reported increased incidence of skeletal malformations in fetuses from rats given ≥93.1 mg/kg bw/day on days 1-21 of gestation. The three lower dose levels, 11.6, 23.3 and 46.6 mg/kg/day all represented NOELs. The NOEL of 46.6 mg/kg bw/day 2-ethoxyethanol would correspond to an equivalent 2-ethoxyethanol acetate dose of 68.5 mg/kg/day. This NOEL is within a factor of ~2 of the NOEL (30.1) estimated from the inhalation teratology data for 2-ethoxyethanol acetate.

Since the inhalation teratology data base for 2-ethoxyethanol acetate is more extensive than the data base for oral 2-ethoxyethanol exposure and since comparison with the oral data indicates that the values agree well and hence the extrapolation error from inhalation to oral exposures is small, the slightly more conservative NOEL (30.1 mg/kg/day) from the inhalation studies is chosen as a basis for ADI estimation.

Taking the highest NOEL of 21.5 mg/kg/day and dividing by 100 (10 to account for interspecies extrapolation and 10 to protect the more sensitive individuals of the human population), an ADI of 0.301 mg/kg/day or 21.1 mg/day for a 70 kg man can be calculated. This daily intake should be sufficiently protective against the harmful fetal effects of 2-ethoxyethanol acetate. The corroborative data on 2-ethoxyethanol indicate that this ADI should provide adequate protection for other endpoints as well.

9. REPORTABLE QUANTITIES

This chapter will only discuss data regarding 2-ethoxyethanol acetate since information pertaining to other 2-ethoxyethanol esters were not found in the available literature as cited in the Appendix.

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Relevant studies pertaining to 2-ethoxyethanol acetate toxicity are summarized in Table 9-1. The data quite clearly indicate that the fetus is significantly susceptible to inhalation exposure during organogenesis. Doe (1984) reported that pregnant rabbits exposed to 100 ppm 6 hours/day during gestation days 6-18 had fetuses with depressed weights and minor skeletal defects; offspring from doses exposed to 400 ppm presented indications of increased embryolethality, teratogenicity, and fetotoxicity; while the mothers also expressed signs of toxicity. The transformed daily doses of 71 and 284 mg/kg/day are multiplied by the cube root of the body weight ratio (3.8 kg for rabbits, 70 kg for man) and by 70 kg to yield human MEDs of 1982 and 7527 mg/day, respectively. These doses correspond to an RV_d of 1.0, which is multiplied by RV_es of 8 (fetotoxicity) and 10 (embryolethality) resulting in CS values of 8.0 and 10.0, respectively. Both of these CSs fall in the range of 1000 for an RQ score.

Because of the similarity in study design, species used and reported results, analagous CS and RQ values are obtained from the other studies investigating 2-ethoxyethanol acetate's fetal effects. Nelson et al. (1984) observed fetotoxicity in rats exposed to 130 ppm, 7 hours/day, on days 7-15 of gestation and more severe effects (teratogenicity, embryolethality) at 390 ppm. Human MEDs of 1556 and 4668 mg/day (using 0.35 kg for rats in the

TABLE 9-1

Toxicity Summary for 2-Ethoxyethanol Acetate

Route	Species/ Strain	Sex	No. at Start	Vehicle/ Physical State	Purity	Dosage/ Exposure	Dose (mg/kg/day)	Response	Reference
Oral	mouse/ JCL-ICR	M	5	water	NR	1000 mg/kg/ day, 5 days/ week, 5 weeks	714	testicular atrophy	Nagano et al., 1979, 1984
						2000 mg/kg/ day, 5 days/ week, 5 weeks	1429	testicular atrophy; leukopenia	Nagano et al., 1979, 1984
Inhalation	rat/Wistar	M,F	40	vapor	≥99%	200 ppm 4 hours/day, 5 days/week, 10 months	82	tubular nephritism males	Truhaut et al., 1979
	rabbit/NZ	M,F	4				68	tubular nephritis	Truhaut et al., 1979
	rabbit/ Dutch	F	24			100 ppm 6 hours/day gestation days 6-18	71	fetotoxicity; no maternal toxicity	Doe, 1984
						400 ppm 6 hours/day gestation days 6-18	284	fetotoxicity; teratogenicity; embryotoxicity; maternal toxicity	Doe, 1984
	rat/SD	F	15		98-99.5%	130 ppm; 7 hours/day; gestation days 7-15	130	fetotoxicity; no maternal toxicity	Nelson et al., 1984
						390 ppm; 7 hours/day; gestation days 7-15	390	fetotoxicity; teratogenicity; embryotoxicity; maternal weight reduction	Nelson et al., 1984
			9			600 ppm 7 hours/day gestation dasy 7-15	600	100% resorptions; maternal toxicity	Nelson et al., 1984

TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	No. at Start	Vehicle/ Physical State	Purity	Dosage/ Exposure	Dose (mg/kg/day)	Response	Reference
Inhalation	rat/F344	F	30	vapor	99.8%	100 ppm 6 hours/day gestation days 6-15	86	fetotoxicity; maternal toxicity	Union Carbide, 1984
						200 ppm 6 hours/day gestation days 6-15	172	teratogenicity; fetotoxicity; maternal toxicity	Union Carbide, 1984
						300 ppm 6 hours/day gestation days 6-15	258	teratogenicity; fetotoxicity; embryotoxicity; maternal toxicity	Union Carbide, 1984
	rabbit/NZ	F	24	vapor	99.8%	100 ppm 6 hours/day gestation days 6-18	71	fetotoxicity; maternal toxicity	Union Carbide, 1984
						200 ppm 6 hours/day gestation days 6-18	142	fetotoxicity; embryotoxicity; teratogenicity, maternal toxicity	Union Carbide, 1984
						300 ppm 6 hours/day gestation days 6-18	213	same as above	Union Carbide, 1984

body weight ratio) are calculated, which give an RV_d of 1.0, respective RV_es of 8 and 10, and respective CS values of 8.0 and 10.0, which yield an RQ of 1000 for both doses.

Comparable CS values ranging from 8.0-10.0 using both rats and rabbits are calculated from the Union Carbide (1984) study. Doses of 100 ppm, 6 hours/day, resulted in fetotoxicity in both species. Human MEDs are calculated to be 1029 mg/day from the rat data and 1982 mg/day from the rabbit data. These MEDs correspond to an RV_d of 1.0, which is multiplied by 8 (RV_e for fetotoxicity) to give a CS of 8.0 and an RQ of 1000. A dose of 200 ppm in rats resulted in teratogenicity and maternal toxicity in rats (RV_e of 9). The effects were somewhat more severe in rabbits, resulting in embryolethality and an RV_e of 10. These values correspond to CSs of 9.0 for rats and 10.0 for rabbits. At 300 ppm, rat fetuses also experience increased incidences of intrauterine death yielding an RV_e of 10 and a CS of 10.0. An RQ of 1000 is warranted for all CS values obtained from this study.

Nagano et al. (1979, 1984) established 714 mg/kg/day for 5 weeks as a dose minimally effective in eliciting testicular atrophy in mice. A human MED of 377 (including a safety factor of 10) is calculated, which corresponds to an RV_d of 1.6. A CS of 9.8 is obtained by multiplying 1.6 by an RV_e of 6 resulting in an RQ of 1000. Truhaut et al. (1979) observed tubular nephritis in rabbits and male rats at a dose of 200 ppm administered 4 hours/day, 5 days/week for 10 months. This study did not use another dose level, thus precluding derivation of a CS and RQ.

Table 9-2 summarizes the studies used to derive RQ values. The highest CS is 10.0, calculated from data obtained in three separate studies using rats and rabbits. Although all studies are extremely similar in experimental protocol, the lowest MED of 3088 mg/day obtained from rat data (Union Carbide, 1984) will be recommended. This dose corresponds to an RV_d of 1.0 and an RV_e of 10. This results in a CS of 10.0 and an RQ of 1000 (Table 9-3).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

There is no data available concerning the carcinogenicity or mutagenicity of 2-ethoxyethanol acetate. According to the IARC classification, 2-ethoxyethanol acetate should be classified as a Group 3 compound, indicating that the data are inadequate to determine the carcinogenicity of 2-ethoxyethanol acetate at this time.

TABLE 9-2

Composite Scores for Toxicity of 2-Ethoxyethanol Acetate

Route	Species	Dose/Exposure	Human MED* (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Oral	mouse	1000 mg/kg/day 5 days/week 5 weeks	377	1.6	testicular atrophy	6	9.6	1000	Nagano et al., 1979, 1984
Inhalation	rabbit	100 ppm 6 hours/day gestation days 6-18	1882	1.0	fetotoxicity; no maternal toxicity	8	8.0	1000	Doe, 1984
		400 ppm 6 hours/day gestation days 6-18	7527	1.0	fetotoxicity; teratogenicity; embryotoxicity; maternal toxicity	9	9.0	1000	Doe, 1984
	rat	130 ppm 7 hours/day gestation days 7-15	1556	1.0	fetotoxicity; no maternal toxicity	8	8.0	1000	Nelson et al., 1984
		390 ppm 7 hours/day gestation days 7-15	4668	1.0	fetotoxicity; teratogenicity; embryotoxicity; maternal toxicity	9	9.0	1000	Nelson et al., 1984
		100 ppm 6 hours/day gestation days 6-15	1029	1.0	fetotoxicity; maternal toxicity	8	8.0	1000	Union Carbide, 1984
Inhalation	rat	200 ppm 6 hours/day gestation days 6-15	2059	1.0	teratogenicity; fetotoxicity; maternal toxicity	9	9.0	1000	Union Carbide, 1984
		300 ppm 6 hours/day gestation days 6-15	3088	1.0	teratogenicity; fetotoxicity; embryotoxicity; maternal toxicity	9	9.0	1000	Union Carbide, 1984

TABLE 9-2 (cont.)

Route	Species	Dose/Exposure	Human MED* (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Inhalation (cont.)	rabbit	100 ppm 6 hours/day gestation days 6-18	1882	1.0	fetotoxicity; maternal toxicity	8	8.0	1000	Union Carbide, 1984
		200 ppm 6 hours/day gestation days 6-18	3764	1.0	fetotoxicity; embryotoxicity;	10	10.0	1000	Union Carbide, 1984

*Dose levels established in animal studies of subchronic duration (120 days or less) were corrected by a factor of 10 to extrapolate to a chronic human MED. Those studies involving gestational exposures are considered to contain doses chronic to the life of the fetus thus precluding the use of a safety factor.

TABLE 9-3

2-Ethoxyethanol Acetate

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	Inhalation
Dose*:	3088 mg/day
Effect:	increased incidence of visceral and skeletal variants and malformations; decreased fetal body weight; increased nonviable implants/litter
Reference:	Union Carbide, 1984
RV_d:	1.0
RV_e:	10
Composite Score:	10.0
RQ:	1000

*Equivalent human dose

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in February, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

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